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$InCl_3$-Catalyzed Allylic Friedel−Crafts Reactions toward the Stereocontrolled Synthesis of 1,2,3,4-Tetrahydroquinolines

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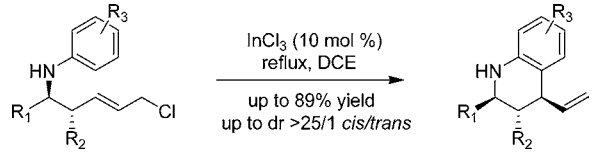
ABSTRACT



Allyl chlorides tethered to an *N*-aryl moiety readily undergo $InCl_3$-catalyzed Friedel−Crafts reactions to furnish highly enantiomerically enriched 1,2,3,4-tetrahydroquinolines with good yields and excellent diastereoselectivity.

1,2,3,4-Tetrahydroquinolines are central subunits in a broad range of natural products and medicinal agents which display interesting biological and pharmacological properties.[1] Accordingly, a wealth of synthetic methods has been developed for the stereoselective synthesis of these heterocycles.[2] Most prominent among them are metal- and Brønsted acid-catalyzed, enantioselective hydrogenations of quinolines[3] as well as enantioselective aza Diels−Alder reactions of aryl imines and electron-rich alkenes (Povarov reaction)[4] and those of in situ generated aza-xylylenes and electron-rich dienophiles.[5] Other methods including ring expansion reactions,[6] asymmetric Reissert reactions,[7] Heck-type cyclizations,[8] organocatalytic hydroarylations of enals,[9] sequential aza-Michael−Mannich reaction of *ortho*-amino benzaldehydes and enals,[10] Pd-catalyzed hydroaminations of anilino alkynes,[11] intramolecular redox reactions,[12] and the carbo-

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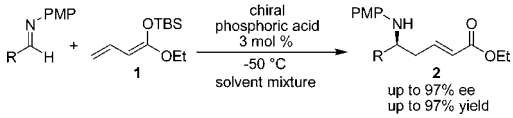
lithiation of unsaturated *ortho*-iodo anilines[13] have been developed additionally to access tetrahydroquinolines in optically enriched form. Recently, Lautens and co-workers reported a powerful palladium-catalyzed cyclization of allyl acetates tethered to an *N*-aryl iodide giving rise to a variety of 2,4-disubstituted tetrahydroquinolines in good yields and perfect 2,4-trans-diastereoselectivity, albeit as racemic mixtures.[14]

We report herein a straightforward and highly stereoselective approach for the synthesis of chiral, highly optically enriched 2,4-disubstituted and 2,3,4-trisubstituted tetrahydroquinolines through a metal-catalyzed, intramolecular Friedel−Crafts-type reaction of allyl chlorides tethered to an *N*-aryl moiety. Complementary to the Lautens process, this new allylic alkylation reaction proceeds in a highly cis-stereoselective fashion and does not require a halogen substituent on the aryl ring.

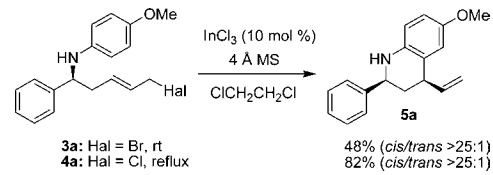
We have recently developed the Brønsted acid-catalyzed, highly enantioselective, vinylogous Mukaiyama−Mannich reaction of vinylketene silyl-*O*,*O*-acetals **1** furnishing δ-amino-α,β-unsaturated esters **2** with excellent enantioselectivity (Scheme 1).[15] With γ-substituted dienolates a second stereogenic center was formed with good anti-diastereoselectivity. As a first synthetic application of the Mannich products obtained in this way, we recently reported a four-step synthesis of the tobacco alkaloid *S*-anabasine in optically highly enriched form.[16]

Scheme 1. Chiral Brønsted Acid-Catalyzed Vinylogous Mukaiyama−Mannich Reaction



In an effort to document further the synthesis potential of the highly functionalized Mannich products, we speculated that we could employ the *N*-aryl group not just as a nitrogen protecting group but incorporate it into the target structure through a Friedel−Crafts-type cyclization to form 1,2,3,4-tetrahydroquinolines. Specifically, we envisaged that conversion of the enoate moiety within **2** into an allylic halide through Dibal-H reduction and halogenation would form a suitable allylic electrophile that was expected to undergo an intramolecular, metal-catalyzed allylic alkylation reaction with the electron-rich *N*-aryl group (Scheme 2).[17]

Scheme 2. Friedel−Crafts Reaction of Allyl Halides **3a** and **4a**



In addition to other Lewis acids commonly employed in Friedel−Crafts reactions, $InCl_3$ has specifically been introduced as a catalyst for the intermolecular[18] and intramolecular[19] reaction of arenes with allyl acetates and allyl bromides, respectively. Accordingly, we prepared both allyl bromide **3a** and allyl chloride **4a** starting from vinylogous Mannich product **2a** in good yields using standard methods (see Supporting Information) and treated them with catalytic amounts of $InCl_3$ and powdered 4 Å molecular sieves in 1,2-dichloroethane.

Friedel−Crafts cyclization of **3a** was very rapid even at ambient temperature and furnished tetrahydroquinoline **5a** in moderate yield (cis/trans > 25:1) along with some unidentified byproducts (Scheme 2). In fact, **3a** proved to be so reactive that it partially cyclized during its preparation. On the other hand, Friedel−Crafts reaction of allyl chloride **4a** was a much cleaner process and delivered **5a** in 82% isolated yield as a single diastereomer (cis/trans > 25:1) with 95% ee after refluxing a solution of **4a** for 18 h in 1,2-dichloroethane. We assume that the catalytic activity of $InCl_3$ in this reaction rests on its halophilic nature activating the allyl system via chloride abstraction.[20] Only trace amounts of **5a** were obtained in the absence of $InCl_3$.

With optimal conditions for the cyclization in hand, a series of vinylogous Mannich products **2b**−**n**, which were prepared in optically highly enriched form using our Brønsted acid-catalyzed process, was converted into allyl chlorides **4b**−**n** via the above-mentioned reduction−halogenation sequence. Subsequently, they were cyclized with $InCl_3$ as catalyst (10 mol %) in the presence of 4 Å molecular sieves to furnish 1,2,3,4-tetrahydroquinolines **5b**−**n** in typically good yields and up to >25:1 diastereoselectivity in favor of

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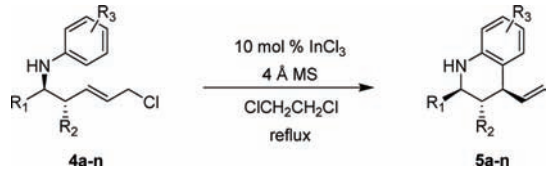
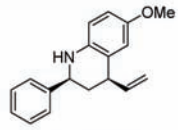
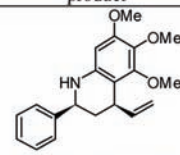
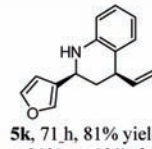
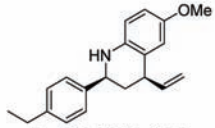
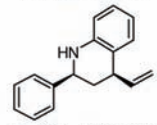
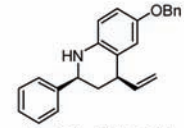
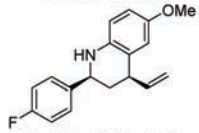
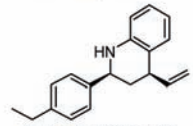
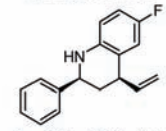
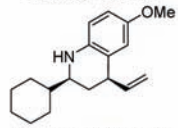
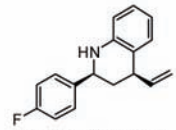
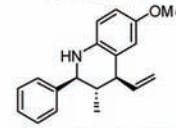
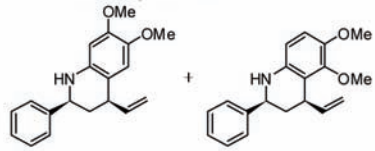
Table 1. Intramolecular $InCl_3$-Catalyzed Friedel−Crafts Reaction[a]



entry	product[b]	entry	product[b]	entry	product[b]
1	 **5a**, 18 h, 82% yield, 95% *ee*, >25/1 *dr*	6	 **5g**, 15 h, 88% yield, 77% *ee*, >25/1 *dr*	10[c]	 **5k**, 71 h, 81% yield, 91% *ee*, 12/1 *dr*
2[c]	 **5b**, 46 h, 77% yield, 97% *ee*, 19/1 *dr*	7[c]	 **5h**, 62 h, 74% yield, 95% *ee*, 13/1 *dr*	11[c]	 **5l**, 64 h, 67% yield, 93% *ee*, 12/1 *dr*
3	 **5c**, 20 h, 73% yield, 91% *ee*, >25/1 *dr*	8[c,d]	 **5i**, 96 h, 70% yield, 98% *ee*, 10/1 *dr*	12[c,e]	 **5m**, 93 h, 58% yield, 95% *ee*, 4/1 *dr*
4	 **5d**, 14 h, 89% yield, 87% *ee*, >25/1 *dr*	9[c]	 **5j**, 88 h, 71% yield, 94% *ee*, 15/1 *dr*	13	 **5n**, 15 h, 81% yield, 95% *ee*, 15/1 *dr*
5	 **5e**, 16 h, 64% yield, 89% *ee*, 14/1 *dr* + **5f**, 16 h, 11% yield, 89% *ee*, >25/1 *dr*				

[a] Reactions were performed with allyl chloride **4** (0.30 mmol, 1.00 equiv), $InCl_3$ (0.03 mmol, 0.10 equiv), and 4 Å molecular sieves under reflux in anhydrous 1,2-dichloroethane (2.0 mL). [b] Yields refer to chromatographically purified material. Enantiomeric excesses were determined by chiral HPLC and were identical for vinylogous Mannich products **2** and tetrahydroquinolines **5** (see Supporting Information); diastereomeric ratios were determined by ^{1}H NMR spectroscopy or HPLC. [c] K_2CO_3 (3.0 equiv) was added. [d] 20 mol % of $InCl_3$ was used. [e] 25 mol % of $InCl_3$ was used.

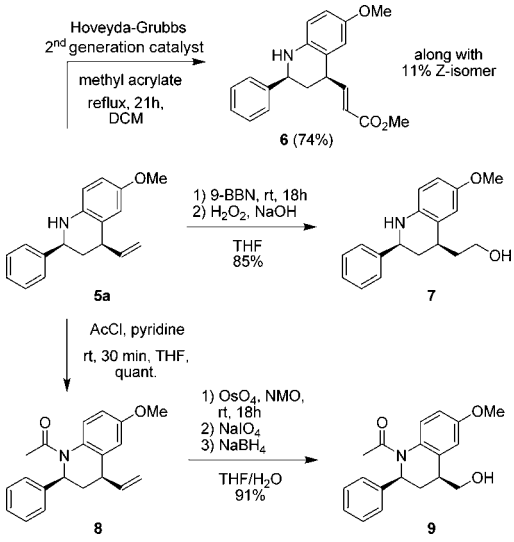
the 2,4-cis-diastereomer (Table 1). The configurational assignment was based upon the characteristic coupling constants in the ^{1}H NMR spectrum. The exceptionally high diastereoselectivity in favor of the 2,4-cis-isomer is believed to originate from the favorable pseudoequatorial positions of the substituents in the transition state of the cyclization.

Whereas substrates with alkoxy-substituted *N*-aryl groups reacted rather quickly, those with *N*-aryl groups lacking any further electron donation or carrying electron-withdrawing substituents required extended reaction times at elevated temperatures and occasionally increased catalyst loadings (entries 8 and 12). Also, the addition of 3 equiv of K_2CO_3 to the reaction mixture was beneficial in those cases to neutralize the in situ generated HCl, which slowly led to decomposition of the starting materials (entries 7−12). Furthermore, the reaction could be successfully extended to the preparation of the 2,3,4-trisubstituted tetrahydroquinoline **5n**, which was obtained in 81% yield and 15:1 cis/trans-diastereoselectivity (entry 13).

It is important to note that due to the modular-type three-component vinylogous Mannich reaction a variety of tetrahydroquinolines with different substituents both in the aromatic portion of the heterocycle as well as in the 2- and 3-positions are accessible in highly enantiomerically enriched form. 2-Alkyl-, 2-aryl-, and 2-heteroaryl-substituted tetrahydroquinolines were all obtained in good yields and typically excellent diastereoselectivity.

Moreover, the vinyl substituent intrinsically present in the 4-position of the heterocyclic skeleton offers some interesting possibilities for modification (Scheme 3). Thus, cross me-

Scheme 3. Elaboration of Tetrahydroquinolines **5a**



tathesis employing the Hoveyda−Grubbs second-generation catalyst[21] furnished α *β*-unsaturated ester **6** in 74% yield along with 11% of the readily separable *Z*-isomer. Furthermore, hydroboration[22] followed by oxidative workup afforded tetrahydroquinoline alcohol **7** in 85% yield. Finally, oxidative degradation of the vinyl group was readily accomplished after conversion into *N*-acetyl tetrahydroquinoline **8** through a sequence comprising dihydroxylation,[23] diol cleavage, and reduction to provide tetrahydroquinoline alcohol **9** in excellent overall yield.

In conclusion, we have developed a novel, flexible, and highly stereoselective process for the synthesis of a broad range of 1,2,3,4-tetrahydroquinolines through an $InCl_3$-catalyzed Friedel−Crafts reaction. Allyl chlorides with both electron-rich and electron-poor *N*-aryl groups successfully underwent the cyclization with high 2,4-cis-diastereoselectivity, delivering products with diverse substitution patterns. An additional key element of the strategy is the Brønsted acid-catalyzed vinylogous Mannich reaction to provide the substrates in highly optically enriched form.

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Supporting Information Available: Detailed experimental procedures, characterization, and copies of spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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